REMARKS

Status of the Claims

Claims 23, 25-27, 30-34, 36, 38-48, 50-58 and 62-66 are pending.

Claims 23, 25-27, 30-34, 36, 38-48, 50-58 and 62-66 have been canceled.

Claims 23, 30 and 42 have been objected to.

By way of this amendment, claims 23, 30, 31, 42 and 48 have been amended, claims 38, 41, 57 and 58 have been canceled, and new claim 67 has been added.

Upon entry of this amendment, claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 will be pending

Summary of the Amendment

Claims 23, 42 and 48 have been amended to incorporate the limitations of claims 41, 57 and 58, respectively. In addition, claims 23 and 42 have been amended to add the limitation that "said peptides that bind to ST receptor activate guanylyl cyclase C." Claims 42 and 48 have also been amended to delete reference to imaging agents. Support for the amendment is found throughout the specification such as on page 5, lines 35-36, page 9, lines 31-35, page 14, lines 15-17, and pages 28-30.

Claims 23, 30 and 42 have been amended to correct obvious typographical errors

Claim 31 has been amended to delete an error which was introduced in the previous amendment. A term was inadvertently added into claim 31 by a clerical error. As amended, the term, which did not appear in earlier versions of the claim, has been deleted.

Claim 38 has been canceled as being redundant.

Claims 41, 57 and 58, have been canceled as being redundant in view of the amendment of claims 23, 42 and 48.

New claim 67 is dependent on claim 48 and further limits the claim to peptides that bind to ST receptor and activate guanylyl cyclase C. Support for the amendment is found throughout the specification such as on page 5, lines 35-36, page 9, lines 31-35 and page 14, lines 15-17.

No new matter has been added.

Claim Objections

Claims 23, 30 and 42 have been objected to for containing informalities. Applicant has amended each of claims 23, 30 and 42 to remove the typographical errors upon which the objection has been based. Applicant respectfully requests that the objection of claims 23, 30 and 42 be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph

Claims 23, 25-27, 30-34, 36, 38-48, 50-58 and 62-66 have been rejected under 35 U.S.C. §112, first paragraph, because, it has been asserted, the specification, while being enabling for using the pharmaceutical compositions in isolated cells, does not reasonably provide enablement for pharmaceutical uses in animals or humans. Applicant respectfully disagrees.

Citing Cianfrocca et al., which disclosed limited success in a Phase I trial on cancer treatment using a peptide drug, the Official asserts that utilization of peptides as pharmaceutical composition (especially administering to human) is highly unpredictable. Applicant urges that Cianfrocca et al. supports a finding of enablement. Cianfrocca et al. conclude that the results from a Phase I testing of a 5 amino acid anti-angiogenic peptide were positive and that the drug should proceed with further clinical testing. The results in Cianfrocca et al reflect that the drug provided benefit a significant fraction of the patients who had otherwise untreatable disease. Nothing in Cianfrocca et al supports a question of the enablement of the claimed invention. The Office notes that peptide drugs may be toxic, that pre-clinical animal model testing and clinical

trials are required to evaluate toxicity and efficacy of a peptide drug, and that adverse effects of peptide pharmaceuticals cannot be generalized, and are highly unpredictable. Applicant urges that the requirement for pre-clinical animal model testing and clinical trials to evaluate toxicity and efficacy of a peptide drug is based upon standards established by the Food and Drug Administration to determine whether a drug product is safe and effective before it can be marketed. The standard is not the same as that which is required to establish enablement and it is improper to use the FDA standard in an evaluation of patentability. The test for enablement under the patent law is whether on skilled in the art, armed with Applicant's specification, could practice the claimed invention without undue experimentation. Nothing in Cianfrocca et al. supports the conclusion that one of skilled in the art would be required to employ undue experimentation to practice the claimed invention. The specification discloses that the peptides have *in vitro* activity. One skilled in the art would expect that the peptides would have some level of activity *in vivo*. Such a level of activity may not be sufficient to support approval of to market a drug but would meet the standard of enablement for patentability. Likewise, the level of toxicity associated with a drug is considered as part of a risk/benefit analysis in the treatment of certain diseases along with other factors such as the lethality of the condition to be treated and availability of alternative therapies. Nothing in Cianfrocca et al suggests that peptides are typically so toxic that there toxicity would make their suitability for use as a cancer therapeutic unpredictable. On the contrary, Cianfrocca et al clearly shows that peptides can be viable drugs.

The Office cites Russell-Jones as evidence that one skilled in the art would not consider the claimed invention enabled because peptide drugs administered orally are subject to proteolysis, making them less bioavailable when delivered orally, and self-administration by non-oral routes are more difficult and traumatic. Russell-Jones is insufficient to establish that one skilled in the art could not practice the claimed invention without undue experimentation. Nevertheless, the limitations of claims 41, 57 and 58 refer to the compositions being injectable.

The citation of Russell-Jones as evidence of unpredictability does not apply to the subject matter of these claims. To advance prosecution, Applicant has amended claims 23, 42, and 48 to incorporate the limitations of claims 41, 57 and 58, respectively. As amended, each pending claim now includes the limitation that the composition is an injectable composition. Accordingly, the issue raised by the Office relying on Russell-Jones is moot.

El-Andaloussi et al (Current Pharmaceutical Design. Vol. 11: 3597-3611; 2005; cited previously), is cited in the Official Action in support of the assertion that the invention is not enabled because delivery of peptide drugs to the inside of cells to exert their pharmaceutical effects is not predictable because the cell membrane prevents entry of peptides into cells. The Office asserts that the instant specification has not shown that the claimed peptides can penetrate cells, or demonstrating their specific cell-penetrating structures and/or properties. The problems disclosed in El-Andaloussi are not present in the delivery of the peptides in the present invention. The peptides specifically bind to ST receptors, which allows the peptides to specifically overcome the problems discussed in El Andaloussi et al. As noted on page 9, lines 29-31 of the specification, the peptides of the instant invention specifically bind to a receptor (ST receptor) which is present on the cell membrane that is exposed to the outside of the cell, after which the receptor and bound ligand are internalized. One skilled in the art recognizes that ST receptors are cellular receptors and that the problems discussed in El Andaloussi are not issues in the enablement of the present invention. Applicant urges that El Andaloussi et al. does not support a finding of non enablement.

The Office cites Voskoglou-Nomiko et al (Clinical Cancer Research. Vol. 9: 4227-4239; 2003) in support of the position that *in vitro* testing for treatment of diseases such as cancer cannot be reliably correlated to successful treatments in animals or humans. It is asserted that, based upon a review of Phase II outcomes using anti-cancer compounds found to be active *in vitro,* correlating *in vitro* cell data to human clinical outcome is highly unpredictable. Applicant

urges that one skilled in the art, viewing Voskoglou-Nomiko et al., would conclude that *in vitro* data, while not definitive, is useful in assessing trends. Voskoglou-Nomiko et al state on page 4237 that "[t]he work presented here argues for emphasis to be placed on *in vitro* cell lines…" In the Conclusions section of the Abstract on page 4227, Voskoglou-Nomiko et al states

> These results suggest that under the right framework and when panels are used, the in vitro cell line and human xenograft models may be useful in predicting the Phase II clinical trial performance of cancer drugs.

Applicant respectfully urges that one skilled in the art would not conclude that the claimed invention is not enabled in view of Voskoglou-Nomiko et al.

The office urges that one skilled in the art reasonably would not and properly should not accept in vitro results as support for in vivo activity, and that to support the conclusion that the claims are enabled, some evidence correlating in vivo results to in vitro testing at the pertinent time is required. Applicant respectfully urges that it is well settled that the proper standard is whether one skilled in the art would conclude that the claimed invention could be practiced without undue experimentation. Under such standard, the answer is yes, the claimed invention is enabled.

Applicant respectfully requests that the rejection of the claims under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claim 31 has been rejected under 35 U.S.C, 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 contains a term which was introduced in the previous response due to a clerical error. Claim 31 has been amended to delete the term.

Applicant respectfully requests that the rejection of the claim 31 under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejection under 35 U.S.C. §103

Duflot and Gluck

Claims 42 and 57 have been rejected under 35 U.S.C. §103 as being unpatentable over Duflot (U.S. Patent No. 4,999,080) in view of Gluck (U.S. Patent No. 6,040,167).

Duflot discloses vaccines comprising a conjugated peptide that comprises heat stable enterotoxin linked to non-toxic carrier protein. The ST peptides in Duflot are synthesized to be non-toxic (see column 2, lines 27-28, 36-37, 45-46, 51-52 and 56, and column 5, lines 12-15, and column 21, lines 8-10). Duflot renders the peptides non-toxic by blocking cysteine residues which are and were known to be required for ST peptide activity. Moreover, the toxin carrier molecules conjugated to such peptides in Duflot are inactivated by Duflot so as to not be toxic (see column 15, lines 65-67). Accordingly, Duflot teaches ST peptides which are non-toxic and inactivation of any toxin used as a carrier molecules.

Gluck discloses liposomes.

It is asserted that it would have been obvious to combine the vaccines of Duflot with the liposomes of Gluck. Applicant respectfully disagrees.

Claim 42 has been amended to incorporate the limitation of claim 57 and to recite that peptides that bind to ST receptors activate guanylyl cyclase C. Accordingly, Duflot teaches away from the claimed invention. Gluck does not rectify this teaching. The claimed invention is not prima facie obvious in view of the combination of Duflot and Gluck

Applicant respectfully requests that the rejection of claims 42 and 57 under 35 U.S.C.

§103 as being unpatentable over Duflot in view of Gluck be withdrawn.

Duflot, Hussain and Trouet

Claims 23, 25-27, 30, 32-34, 38, 41-43, 45-48, 50-58 and 62-66 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Duflot et al (US Patent 4,499,080; 2/12/1985; cited previously), in view of Hussain et al (EP 0341661: 11/15/1989) and Trouet et al (PNAS. Vol. 79: 626-629; 1982).

Duflot is discussed above.

Hussain discloses conjugation of non-peptides to peptides to stabilize and improve delivery of peptides through the mucosae.

Trouet discloses conjugating non-peptide drugs to peptides to carry and target anti-tumor drugs.

It is asserted that it would have been prima facie obvious to one skilled in the art to make the claimed compositions. It is asserted that one skilled in the art would use a peptide taught in Duflot as a carrier peptide to delivery therapeutic agents such as those taught in Hussain or Trouet. It is asserted that all the references teach pharmaceutical compositions comprising a carrier peptide (or protein) with an active or therapeutic agent for effective drug delivery, so it would have been obvious to one skilled in the art to substitute one agent or one peptide for the other to achieve the predictable result of making a pharmaceutical composition. Applicant respectfully disagrees.

As discussed above, Duflot teaches away from the claimed invention. Duflot teaches that both the ST peptide and any carrier peptides which is toxic are rendered non-toxic to be used in the vaccines described in the Duflot. Specifically, Duflot required that the ST peptide be non-toxic. This is a critical requirement of the invention in Duflot. The instant claims 23 and 42, and the claims dependent there from, specifically require that the peptides which bind to ST do not active GCC, i.e. they are non-toxic. Accordingly, Duflot teaches away from the claimed

invention. Furthermore, Duflot specifically teaches inactivating the toxicity of the carrier molecule. A feature of the claimed invention is that the molecule delivered with the ST binding molecule is a therapeutic agent. Duflot specifically teaches inactivating the activity of the toxic carrier peptide. Duflot specifically teaches away from the claimed invention.

Hussain et al is cited as teaching that addition of a non-peptide carrier molecule to the ST peptide of Duflot. It is asserted that one skilled in the art would do so because Hussain teaches that the addition of the non-peptide carrier improves bioavailability. Hussain et al is directed to absorption enhancers for improving uptake of drugs delivered into mucosal tissue. The claims have been amended to each include the subject matter of one of claims 41, 57 and 58, i.e. that the pharmaceutical composition is an injectable pharmaceutical composition. As such, in addition to claims 41, 57 and 58, Hussain et al. teaches away from each of the pending claims. Specifically, Hussain et al teaches making compounds more amenable to absorption based, non-injection routes of administration. One skilled in the art would not use an absorption enhancer taught by Hussain et al. to modify Duflot in the preparation of an injectable pharmaceutical compositions. Hussain et al. teaches away from combining with Duflot and teaches away from the claimed invention.

Trouet et al. is cited as teaching the conjugation of non-peptide drugs to peptides in order to provide selective targeting of anti-tumor drugs. Trouet et al. discloses linking a known anti-tumor drug to a molecule which selectively binds to another molecule on a tumor cell in order to deliver the anti-tumor drugs to tumor cells. One skilled in the art would not use the tumor targeting taught by Trouet et al. to modify Duflot in the preparation of injectable pharmaceutical compositions of the claimed invention. One skilled in the art would not recognize the benefit of doing so. Only by using the teachings in Applicant's specification would one skilled in the art recognize that injection of pharmaceutical compositions with compounds that bind to ST receptors would target metastasized colorectal tumor cells. It is

impermissible to use Applicant's own disclosure in a finding of obviousness. In the absence of Applicant's teachings, one skilled in the art would see no benefit of replacing the carrier proteins of Duflot with anti-tumor drugs. The reason to do so arises from Applicant's teachings, whose use in impermissible and whose content is necessary to establish a reason why one skilled in the art would combine the teachings of Duflot with Trouet.

The claims are not obvious in view of Duflot et in view of Hussain et al and Trouet et al. Applicant respectfully requests that the rejection of the claims under 35 U.S.C. §103(a) as being unpatentable over Duflot et in view of Hussain et al and Trouet et al. be withdrawn.

Duflot and Others

Claims 23, 25-27, 30-34, 36, 38-48, 50-58 and 62-66 are rejected under 35 U.S.C. §103(a) as being unpatentable over Duflot et al (US Patent 4,499,080; 2/12/1985; cited previously), in view of Hussain et al (EP 0341661; 11/15/1989) and Trouet et al (PNAS. Vol. 79: 626-629; 1982), as applied to claims 23, 25-27, 30, 32-34, 38, 41-43, 45-48, 50-58 and 62-66 above, and further in view of Lee et al (US 5,183,805; 2/2/1993).

Duflot, Hussain et al. and Trouet et al. are each discussed above.

Lee et al. discloses conjugating non-peptide drugs including 5-fluorouracil to peptides for cancer therapeutics.

As noted above, Duflot and Hussain et al. teach away from the claimed invention and Trouet et al. requires the information in Applicant's specification in order to provide any benefit to be recognized by one skilled in the art in combining Trouet as suggested.

Applicant respectfully urges that Lee et al. also requires the information in Applicant's specification in order to establish a prima facie case of obviousness and such use is impermissible. Applicant respectfully urges that only through the use of Applicant's teaching would there be any benefit to be recognized by one skilled in the art for producing an injectable composition which includes ST receptor binding antibodies, fragments thereof or peptides which

bind to ST receptors and therapeutic agents.

The claims are not obvious in view of Duflot et in view of Hussain et al and Trouet et al. and further in view of Lee et al. Applicant respectfully requests that the rejection of the claims under 35 U.S.C. §103(a) as being unpatentable over Duflot et in view of Hussain et al and Trouet et al. and Lee et al. be withdrawn.

Double Patenting Rejection

U.S. Patent Nos. 5,962,220, 6,087,109 and 7,097,839

Claims 23, 25-28, 33, 34, 38 and 40 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5 and 6 of U.S. Patent No. 5,962,220.

Claims 23, 25-28, 33, 34, 38 and 40 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 and 13 of U.S. Patent No. 6,087,109.

Claims 23 and 28 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24, 26, 28, 29 and 33-41 of U.S. Patent No. 7,097,839.

Claims 23, 25-28, 33, 34, 38, 40, 41, 42, 45 and 47 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 10 and 12 of U.S. Patent No. 5,962,220 in view of Gluck.

As noted in previous responses, once claims have been indicated to be allowable, Applicant shall promptly provide Terminal Disclaimer as appropriate. To that end, the Examiner is invited to contact Applicant's undersigned representative and inform him of the allowability of the claims so that a Terminal Disclaimer can be promptly filed.

Provisional Double Patenting Rejection

Claims 23, 25-27, 48, 50, 51, 52, 54 and 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10, 12 and 15-17 and 20-22 of copending Application No. 11/494,901 (US 20060269477). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed invention in the '901 application reads on the instant claimed invention.

This rejection is provisional. As the co-pending application has not yet issued, no action is required at this time.

Conclusion

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are in condition for allowance. A notice of allowability is earnestly requested. Applicant's undersigned representative hereby requests that the Examiner contact him at 610-640-7855 to discuss any unresolved issues and to arrange for the timely filing of any terminal disclaimers upon an indication of allowability of the claims.

The Commissioner is hereby authorized to charge any debit or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

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